

### REMARKS

Claims 1-20 were filed in the original case. Claims 1-20 were cancelled and claims 21-41 were added in a previous amendment. Claims 21-41 were cancelled and claims 42-73 were added in a previous amendment. Claims 42-73 were cancelled in a previous amendment. Claims 74-105 were presented with a previous amendment. Therefore claims 74-105 are currently pending.

In the Office Action dated March 3, 2003, the Examiner has withdrawn rejections from the previous Office Action. However, the Examiner has maintained one rejection. The currently pending rejections is:

- 1) Claims 74-105 stand rejected under 35 U.S.C. §103(a).

Applicant believes that the Examiner has failed to establish a *prima facie* case for obviousness of the pending claims. Therefore claims 74-105 should be passed into allowance.

### CLAIMS 74-105 ARE NON-OBVIOUS

#### I. The Examiner's Rejection is Defective as a Matter of Law

##### A. The Examiner Does Not Provide a Proper Suggestion or Motivation to Combine References

In the Office Action of 03/23/2004 the Examiner has rejected claims 74-105 as allegedly being obvious in view of the combination of nine references. The Examiner argues:

"Claims 42-73 are rejected under 35 U.S.C. §103(a) as being unpatentable over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Quane et al (Human Molecular Genetics, Vol 3, No. 3, page 471-476, 1994) or Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) and Evans et al (Science, Vol 286, pages 487-491, October 1999) or Poort et al (Blood, Vol 88, No 10, page 3698-3703, 1996), and further in view of Hoon et al. (US Pat. 6,057,105, May 2, 2000) and Hacia (Nature Genetics Supplement. Vol. 21, pages 42-47, January, 1999) (Office Action 03/23/2004, page 3).

In the Office Action of 03/23/2004 the Examiner fails to meet the Patent and Trademark Office's legal responsibility to first establish a *prima facie* case of obviousness supported by objective evidence prior to any necessity by the Applicant to rebut the Examiner's position. The Examiner has never provided objective evidence demonstrating a motivation to combine or modify the cited references. Lacking objective evidence, the Examiner fails to apply the proper legal standard of obviousness. The Examiner's addition of Hacia in the Office Action of 03/23/2004 to the impermissible combination of references from previous Office Actions does not remedy these defects. Because the Examiner cannot evade the Patent and Trademark Office's obligation to provide objective evidence of obviousness as a first step, the rejection must be withdrawn.

In Office Action of 03/23/2004, the Examiner cites nine prior art references in reconstructing the present invention guided only by the present invention's Claims and Specification. The Examiner argues:

The art teaches

- A method of performing perioperative screening to provide biological information about the patient within 72 hours of the surgery (Miller)
- Once an individual is diagnosed as being susceptible to MH, the anaesthetics which trigger this syndrome can be avoided (Quane). Mutations are taught which are associated with MH.
- Numerous mutations in numerous genes which are associated with toxicity, decreased or increased efficiency, ineffective to various operative drugs (Quane, De Lu (sic), AAS, Poort, Evans, for example)
- Methods using multiple markers provide increased sensitivity over methods employing single markers.
- Arrays for high-throughput and highly accurate mutational analysis which may be used for as many as 500 mutations.

(Office Action 03/23/2004, page 12)

As pointed out to the Examiner in the Amendment and Response to Office Action, 01/02/2004 (page 19), none of the Examiner's cited references alone or in combination provide a motivation to combine the references to arrive at the present invention. The addition of Hacia in the present Office Action fails to correct the Examiner's error. Specifically, Hacia does not teach, motivate or suggest a combination of references for detection of two or more nucleic acid genetic markers in two or more genes associated with two or more conditions to generate a genomic profile in a sample from a perioperative subject for use in selecting a perioperative course of action. The Examiner's response in the present Office Action to this critical defect in attempting to sustain the rejection consists merely of conclusory remarks unsupported by objective evidence. For example:

"Therefore, the Examiner has provided a combination of references reflecting the state of the art at the time the invention was made which renders the claims obvious and provides explicit motivation for performing such methods as required by the instant claims."  
(Office Action 03/23/2004, page 14) (Emphasis added.)

and:

"The examiner has set forth a prima facie case which combines all of the teachings and motivations specifically enumerated in the art to obtain the claimed invention as a whole (see rejection above)." (Office Action 03/23/2004, page 12). (Emphasis added.)

Applicant asks where is the Examiner's "explicit motivation"? Where are the Examiner's "motivations specifically enumerated"? Instead of providing evidence for a motivation to combine the references, the Examiner simply recites many, but not all, of the benefits of the present invention taking medical and surgical conditions disclosed in the Specification of the present invention one-by-one. (Office Action 03/23/2004, pages 12-14). The Examiner argues:

"The express teaching in Quane that "Once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided" provides

explicit motivation for testing individuals prior to anesthetics to avoid triggering MH.” (Office Action 03/23/2004, page 12).

On page 20 of the Office Action the Examiner’s Quane quotation is re-asserted:

The examiner’s position is not based upon improper hindsight. The art clearly provides motivation. Quane, for example teaches that “once an individual is diagnosed as being susceptible to MH anesthetics which trigger this syndrome can be avoided.” This explicit teaching to avoid anesthetics which trigger MH is motivation to avoid administering anesthetics to patients with particular mutations. Therefore the combination of references is permissible. (Office Action 03/23/2004, page 20). (Emphasis added.)

The Examiner is wrong. The combination is not permissible because the art does not provide motivation to make the combination. Quane relates to only one phenotype or condition, i.e., MH. Alone, or in combination with the Examiner’s other references, Quane does not teach, motivate or suggest a combination of references for detection of two or more nucleic acid genetic markers in two or more genes associated with two or more conditions to generate a genomic profile in a sample from a perioperative subject for use in selecting a perioperative course of action. Quane does not mention, suggest, teach or motivate any combination of references as the Examiner alleges in error.

Indeed, as the Examiner explicitly, and specifically, concedes in the present Office Action:

The claims are drawn to detecting two or more genetic markers to generate a genomic profile useful in selecting (a) perioperative course of action. The claims are not drawn to diagnosing MH. The claims are drawn to screening a patient perioperatively to determine a risk for complications; a method for selecting conditions for a surgical procedure; a method of screening a patient perioperatively to determine a risk for complications during said surgical procedure. (Office Action 03/23/2004, page 18) (Emphasis added)

Thus, the Examiner is expressly aware of the gap between the Examiner's combination of references and the present claims, that is, the absence of a motivation or suggestion to combine the Examiner's cited references to arrive at the present invention. Indeed, the Examiner explicitly acknowledges that Quane does not teach, suggest or motivate the detection of two or more nucleic acid genetic markers in two or more genes associated with two or more conditions to generate a genomic profile in a sample from a perioperative subject for use in selecting a perioperative course of action of the present invention. None of the Examiner's cited references alone or in combination teach, suggest or motivate the perioperative genomic profiles of the present invention.

**B. The Examiner Has Not Answered The Applicant's Request for Evidence of Motivation to Combine the Examiner's Nine References**

In the Office Action of 03/23/2004 the Examiner speculates on what an artisan of ordinary skill would have recognized or been motivated to do. For example:

"The ordinary artisan would have clearly recognized the benefit of testing an individual prior to surgery and subjection to the anesthesia for known genetic markers associated with a condition which was triggered by anesthetics." (Office Action 03/23/2004, page 9).

And

"The ordinary artisan would have been motivated to have screened individuals within two days prior to surgery to determine the genetic composition of the individuals to provide individualized diagnosis." (Office Action 03/23/2004, page 10)

The Examiner's requirement to provide evidence of the motivation to combine the Examiner's references is absolute. (*In re Kotzab*, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000). In the Applicant's most recent Amendment and Response to Office Action mailed 01/04/2004, Applicant pointed out the Examiner's complete lack of supporting

objective evidence sustaining the Examiner's speculations with regard to what an ordinary artisan would or would not have recognized or been motivated to do. (Pages 8-9). In the present Office Action the Examiner's only response to this deficiency is to once again recite the Quane reference as follows:

"With respect to what the ordinary artisan would have recognized or appreciated, Quane teaches that once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided. Quane is at least an ordinary artisan if not a skilled artisan. Quane clearly recognizes the benefit of testing an individual prior to surgery to avoid triggering MH. Thus, the skilled artisan did recognize the benefit of screening individuals prior to surgery to avoid known conditions triggered by particular mutations or markers in genes." (Office Action 03/23/2004, page 18).

At best, Quane provides motivation to test patients after surgery for polymorphisms in a single gene for a single condition. But this is not the motivation the Examiner requires in order to permissibly combine the Examiner's references. In the Office Action of 03/23/2004 the Examiner persists in this confusion. Quane cannot, and does not, provide motivation to combine the Examiner's references because Quane is directed solely to a single gene (i.e., RYR1) and a single condition (i.e., MH). Similarly, none of the remainder of the Examiner's references provide motivation to combine the Examiner's references for obtaining a sample from a perioperative subject scheduled for a surgical procedure that has not yet been completed, and subjecting the sample to an assay for detecting two or more nucleic acid genetic markers in two or more genes associated with two or more conditions to generate a genomic profile for use in selecting a perioperative course of action. Quane has no teaching to make the Examiner's combination. Quane does not mention, teach or suggest any of the other genes or other conditions of the Examiner's other references. Quane provides no reason to combine any of the elements of the Examiner's other references. Nor do any of the Examiner's other references motivate, teach or suggest this combination.

Merely because the references could be combined or modified does not render the resultant combination obvious unless the prior art suggested the combination. MPEP §2143.01; *In re Mills*, 916 F.2d 680, 682, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990). Applicant submits that

the Examiner's references cannot be considered collectively until the Examiner points to some motivation to combine the Examiner's specific references. The purpose behind this obligation is to prevent the Examiner, as here, from using the invention itself together with hindsight reconstruction to defeat the patentability of the invention. Moreover, the law does not regard the Examiner as one skilled in the art. ("[T]he examiner's assumptions do not constitute the disclosure of the prior art." *In re Riejckaert*, 28 USPQ2d 1955 at 1956 (Fed. Cir. 1993). "[W]hen the PTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears." See *Id.* At 1957.) "[B]road, conclusory statements regarding the teachings of multiple references, standing alone, are not 'evidence.'" (*In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614 (Fed. Cir. 1999).

**C. The Examiner must First Establish *Prima Facie* Obviousness and Has Not**

Section 103 of title 35 of the United States Code states:

A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. (35 U.S.C. § 103 (a) (2000).

In assessing the differences between the subject matter sought to be patented and the prior art, section 103 requires the Examiner to appraise the claimed invention "as a whole". Typically inventions are new combinations of existing principles or features.<sup>1</sup> The "as a whole" instruction to the Examiner in title 35 prevents evaluation of the invention piece-by-piece. Without this statutory requirement, the Examiner's obviousness assessment risks breaking an invention into its component parts ( $X + Y + Z$ ), then find a prior art reference containing X, another containing Y, and another containing Z, and on that basis, and no other, declaring the invention obvious. In the Office Action of 03/23/2004 the Examiner has fallen into this trap.

<sup>1</sup> *Env'tl. Designs, Ltd. V. Union Oil Co.*, 713 F.2d 693, 698 (Fed. Cir. 1983) (noting that "virtually all [inventions] are combinations of old elements").

The Examiner's hindsight reasoning in using the invention as a roadmap to locate its prior art components discounts the value of combining existing features and principles in a new way to achieve a new result, that is, the perioperative genomic profiles of the present invention. The Court of Appeals for the Federal Circuit has provided further assurance of an "as a whole" assessment of the invention under §103 by requiring a showing by the Examiner that the prior art provide "a reason, suggestion, or motivation to lead an inventor to combine those references."<sup>2</sup> "The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence"."<sup>3</sup> The suggestion to combine prior art references must come from the cited references, not from the applicant's disclosure."<sup>4</sup>

The Examiner must show a suggestion or motivation before the invention itself to make the new combination, particularly when each of the Examiner's cited references address widely divergent problems (e.g. MH, BChE deficiency, venous thrombosis).

To the contrary, none of the problems addressed by the prior art references are the problem addressed by the present invention, that is, detection of two or more nucleic acid genetic markers in two or more genes associated with two or more conditions to generate a genomic profile in a sample from a perioperative subject for use in selecting a perioperative course of action of the present invention.

In the Office Action of 03/23/2004 the Examiner has constructed a conclusion-oriented discussion that typically accompanies a hindsight analysis. Each of the prior art references is at best a piece or component of the present invention. None of the Examiner's cited references teaches the perioperative genomic profiles of the invention itself. The Examiner has made no factual finding of a motivation to combine the nine teachings of Miller, Quane, Acta Anesthesiologica Scandinavica, La Du, Pharmacogenetics, Evans, Poort, Hoon, and Hacia. Contrary to legal requirement, the Examiner's conclusory and unsupported assertion is not evidence. The Examiner does not, and cannot, point to which specific teachings in the cited references motivate the ordinary artisan to combine the claimed elements thereby arriving at the genomic profiles of the present invention for use in a perioperative subject.

<sup>2</sup> *Pro-Mold and Tool Co. v. Great Lakes Plastics Inc.*, 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

<sup>3</sup> *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999).

<sup>4</sup> *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1998)



Rather, the Examiner's assertions reflect the absence of evidence, and thus do not fulfill the obligation of the Patent and Trademark Office in establishing a *prima facie* case of obviousness. There is no mention of the perioperative genomic profiles of the present invention in the Examiner's cited references. There is no motivation to assemble the perioperative genomic profiles of the present invention in the Examiner's cited references. Nowhere in the prior art of record has the Examiner identified a teaching, suggestion or motivation to detect two or more nucleic acid genetic markers in two or more genes associated with two or more conditions in a sample from a perioperative subject to generate a genomic profile for use in selecting a perioperative course of action. If the Examiner is aware of such a suggestion or motivation the Examiner is required to put it forward, and the Examiner has not. To the contrary, the Examiner has failed to provide any evidence whatsoever for a motivation or suggestion to combine the cited references to arrive at the present invention other than that provided by the Applicant's Specification and Claims. Therefore the rejection must be withdrawn.

**D. The Examiner's Combination of Nine References Does Not Teach All Elements of The Claims**

In the Applicant's prior Amendment and Response to Office Action mailed 01/02/04 it was pointed out to the Examiner that none of the references alone or in combination provide detection of two or more nucleic acid genetic markers in two or more genes associated with two or more conditions to generate a genomic profile in a sample from a perioperative subject for use in selecting a perioperative course of action. (Amendment and Response to Office Action 01/02/2004, page 15). The Examiner argues:

"This argument has been thoroughly reviewed, but is not found persuasive because the general teaching of Hoon provides that multiple markers from multiple genes was more effective than a single marker alone. . . . The teachings of Hoon cover the idea of combining alleles for improved detection sensitivity and the teachings are not limited to the subject matter granted protection in the claims." (Office Action 03/23/2004, page 23).

Hoon teaches the use of one set of markers for detection of one condition (i.e., breast cancer), and a second set of markers for detection of an unrelated condition (i.e., melanoma). Hoon does not teach the elements of detection of two or more conditions in the same subject for the shared purpose of selecting a perioperative course of action. Therefore, the present invention is completely different from, and non-obvious, on the basis of Hoon. The Examiner's addition of Hacia to the previous eight references in the Office Action of 03/23/2004 fails to remedy the missing-elements defect of the present rejection. The Examiner's impermissible combination of Miller, Quane, Acta Anesthesiologica Scandinavica, La Du, Pharmacogenetics, Evans, Poort, Hoon, and Hacia does not teach the genomic profile elements of the present claims, for example, Claim 74 genomic profiles "for use in selecting a perioperative course of action", or Claim 87 genomic profiles "for use in selecting a surgical procedure treatment course of action", or Claim 94 and 101 genomic profiles "for use by a physician in determining a risk for complications during a surgical procedure", or Claim 102 genomic profiles "consulted in selecting an appropriate anesthesia treatment for said subject." Moreover, Hoon plus Hacia does not teach two or more nucleic acid markers in two or more genes for two or more conditions in the perioperative subject of the present claims. Hacia does not teach the categories and selection criteria of genetic markers of the present invention.

Thus, the Examiner's combination of Hacia with previously cited references fails to teach every element of the presently claimed invention and, without more, the Examiner is unable to sustain a *prima facie* case of obviousness. In view of the above, the Applicant respectfully requests that the rejection be withdrawn.

**E. The Examiner's Combination of Nine References Does Not Provide a Reasonable Expectation of Success**

In the Office Action of 03/23/2004 the Examiner observes:

Applicant then argues this is an "obvious to try" situation (page 14).  
(Office Action 03/23/2004, page 21)

The Examiner is in error. The Applicant has not argued the Examiner's "obvious to try" situation on page 14, or elsewhere in the Amendment and Response to Office Action mailed 01/04/2004. The Examiner mistakenly concludes:

In this factual case, there is express suggestion in the prior art that polymorphisms are known to be associated with complications to anesthesia as taught by Quane. There is further evidence as shown by DeLu (sic), Poort, AAS, Evans, for example. This is sufficient for a reasonable expectation of success. . . . The response appears to also argue that there is no reasonable expectation of succession (sic) in using Hoon. This argument has been thoroughly reviewed, but is not found persuasive for the reasons above.

Multiplexing or arraying more than one mutation was well known in the art at the time the invention was made (see Hoon and Hacia) (Office Action 03/23/2004, page 21-22)

To the contrary, the Examiner's combinations are not sufficient for a reasonable expectation of success. Alone, or in combination with other references cited by the Examiner, Hoon and Hacia provide no specific guidance, general guidance, or any guidance whatsoever in selecting two or more nucleic acid markers in two or more genes known to be associated with two or more conditions to generate a genomic profile for use in selecting a perioperative course of action. Therefore, the Examiner cannot advance any evidence in support of the contention that the artisan using the methods of Hacia alone, or in combination with the Examiner's other cited references, would have had a reasonable expectation of success. Because the Examiner is not able to show that a reasonable expectation of success may be found in Hacia, the third prong of a *prima facie* case of obviousness is defective, as are prongs one and two.

**F. The Examiner's Rejection of Claims 74-105 is Defective as a Matter of Law**

A *prima facie* case of obviousness requires the Examiner to cite to a reference which a) discloses all the elements of the claimed invention, b) suggests or motivates one of ordinary skill in the art to combine the claim elements to yield the claimed invention, and c) provides a reasonable expectation of success should the claimed combination be carried out. Failure to establish any one of these three requirements negates a finding of a *prima facie* case and, without

more, entitles the Applicants to allowance of the claims in issue. (MPEP) Because not one, but each of the three elements of a *prima facie* case of obviousness is lacking, the Applicant respectfully requests that the rejection under 35 USC §103(a) for alleged obviousness be withdrawn.

## **II. The Examiner's Rejection is Defective as a Matter of Fact**

In the Office Action of 03/23/2004 the Examiner argues:

"The ordinary artisan would have been motivated to have screened individuals within two days prior to surgery to determine the genetic composition of individuals to provide individualized diagnosis. Thus, the ordinary artisan would have been motivated to test patients within two days prior to surgery for mutations within any of the known genes for known mutations which are associated with known conditions for the expected benefit of determining whether the patient possessed any mutations which were linked to the known conditions such that the clinician may avoid any adverse reactions to the surgical procedure." (Office Action 03/23/2004, page 10).

The Examiner is factually in error. At the time the invention was made skilled artisans were not motivated to test patients for two or more nucleic acid markers in two or more genes known to be associated with two or more conditions to generate a genomic profile for use in selecting a perioperative course of action. The Examiner has proffered an argument for rejection on the basis of obviousness by coupling assertions of the invention's clear-cut and undisputed utility, with incorrect, unsupported and conclusory guesses-in-hindsight about what an ordinary artisan "would have clearly recognized" or "would have been motivated to do". The Examiner's guesses do not satisfy requirements for establishing the *prima facie* case of obviousness. The only source available to the Examiner teaching these assertions is the present disclosure. The Examiner's recognition of benefits of the present invention, made in possession of the Claims and Specification, are no substitute for evidence of what an artisan of ordinary skill would or would not have recognized or been motivated to do at the time the invention was made.

Applicant need not provide any evidence to rebut the Examiner's failure to establish a prima facie case for obviousness, and for the Examiner's mistaken rejection to be overturned. Yet Applicant has provided evidence. In order to further prosecution of the present case, and while under no legal obligation to do so, the Applicant has provided ample, specific and objective evidence in the form of published references, peer reviews, a Declaration, and a Practice Advisory. Contrary to the Examiner's speculations, this evidence documents that at the time the invention was made, ordinary artisans did not agree with the Examiner regarding the obviousness of perioperative genomic profiles.

In the Office Action of 03/23/2004 the Examiner has mischaracterized and dismissed, but not contradicted, this evidence demonstrating that the Examiner's speculations are in error. Despite the Examiner's mischaracterizations and misconstructions of this evidence, these facts remain uncontested.

**A. The Anesthesia Patient Safety Foundation (APSF) Review Stands for Non-Obviousness**

With regard to the APSF review of a grant application entitled "Perioperative Genomic Profiles" the Examiner argues: "The committee does not appear to be establishing that given the art at the time of the filing, that the invention was non obvious". (Office Action 03/23/2004, page 15). To the contrary, that is exactly what the APSF review committee asserts:

"The APSF committee members reviewing your proposal to study genetic profiles were impressed by the elegance to the proposal. It would take the issue of patient safety in a new direction." (Declaration of Kirk Hogan, M.D., 02/08/2002).

Hence, skilled artisans state that the present invention is non-obvious.

**B. Gregory, Kirby and Hopkins Stand for the Non-Obviousness of the Present Invention**

In the Office Action of 03/23/2004 the Examiner argues: "The response provides three

references directed to the proposition that routine perioperative testing is unnecessary.” (Office Action 03/23/2004, page 16). Rather, the three references direct the Examiner to the proposition that testing patients for two or more nucleic acid markers in two or more genes known to be associated with two or more conditions to generate a genomic profile for use in selecting a perioperative course of action was non-obvious to artisans of ordinary skill at the time the invention was made. If, as the Examiner contends, the prior art had contemplated the perioperative genomic profiles of the present invention they would have been taught, suggested or mentioned in Gregory, Kirby and Hopkins. They are not.

**C) The Second Declaration of Kirk Hogan, M.D., and the “Practice Advisory for Preanesthesia Evaluation: A Report by the American Society of Anesthesiologists Task Force on Preanesthesia Evaluation”, Stand for the Non-Obviousness of the Present Claims**

In the Office Action of 03/23/2004 the Examiner argues:

“The declaration asserts that no perioperative genetic testing of any kind is advocated, discussed or mentioned. This silence with respect to genetic testing does not mean that the testing would be unobvious. While the article may not specifically consider genotypes for preanesthesia evaluation [it] does not provide evidence that the combination of the cited references do not provide the legal standard for obviousness.” (Office Action 03/23/2004, page 18).

Applicant reminds the Examiner that it is not the Applicant’s duty to prove non-obviousness. Rather, the Examiner must first provide objective evidence of obviousness to establish a *prima facie* case of obviousness in the first instance. To the contrary, the 2002 Practice Advisory’s silence on the matter of genetic testing in the perioperative interval directly contradicts the Examiner’s assertions. The Practice Advisory, and all other objective evidence of record, stands in simple contrast to the Examiner’s lack of evidence and erroneous suppositions regarding what an ordinary artisan might have clearly recognized or been motivated to do. In other words, given the impossible task of showing that the art had not thought of something that

had not yet been created, Applicant has (although not required to) provided evidence that tends to show that, to the extent artisans have addressed the issue (even after the filing of the present invention), there has been no motivation to move in the direction of the presently claimed invention.

To assist the Examiner, the Applicant has put forward objective, specific, ample and easily understood evidence showing the Examiner's inability to fabricate a *prima facie* case of obviousness. In the Office Action of 03/23/2004 the Examiner has dismissed, but not contradicted, this evidence. As detailed above, to sustain the rejection the Examiner must put forth actual objective evidence. Instead, the Examiner has inappropriately concluded that because the invention is very useful, it must therefore be obvious. On the current evidence of record the Examiner's rejections cannot stand. If the Examiner is unable to provide the required evidence, but sustains the rejection, the Examiner will be unfairly and inappropriately delaying allowance of the present case. For these reasons Applicant respectfully requests that the rejections be withdrawn.

### **III. Claims 84, 85, 92, 93, 99 and 100 are Allowable**

In the Office Action of 03/23/2004 the Examiner argues:

"With respect to the claims drawn to specific numbers of markers, for example 5 and 10 or more mutations, the skilled artisan would be motivated to screen markers which were well known at the time of the art simultaneously or in tandem for the benefits of providing the most complete amount of information possible. Hacia specifically teaches that arrays to detection mutations (sic) of approximately 500 were known in the art at the time the invention was made." (Office Action 03/23/2004, Page 11)

The Examiner's assertion is conclusory and unsupported by objective, factual evidence. The Examiner does not specify what text of Hacia the Examiner considers to be the closest prior art for 5 or more, or 10 or more nucleic acid genetic markers in two or more genes associated with two or more conditions to generate a genomic profile for use in selecting a perioperative course of action. The Examiner does not specify what text in Hacia, or any other

of the Examiner's references, would guide the skilled artisan to "screen markers well known at the time of the art" for inclusion in a genomic profile for use in selecting a perioperative course of action, other than guidance provided by the present invention's Specification and Claims.

#### **IV. Claim 101 is Allowable And Has Not Been Examined**

In the Office Action of 03/23/2004, the Examiner argues:

"With respect to what the ordinary artisan would have recognized or appreciated, Quane teaches that once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided. Quane is at least an ordinary artisan if not a skilled artisan. Quane clearly recognizes the benefit of testing an individual prior to surgery to avoid triggering MH. Thus, the skilled artisan did recognize the benefit of screening individuals prior to surgery to avoid known conditions triggered by particular mutations or markers in genes." (Office Action 03/23/2004, page 18)

The Examiner makes a number of errors. First, Quane does not "clearly recognize the benefit of testing prior to surgery". In fact, Quane's subjects are tested following surgery i.e., a muscle biopsy. Quane's patients were tested after surgery to identify a genetic polymorphism. In contrast to the presently claimed invention, Quane's subjects were not tested in the perioperative period as claimed, nor would Quane's subjects be tested in the perioperative period as claimed for future surgery as they would have already been characterized. Therefore, contrary to the Examiner's guess, there is no teaching in Quane to conduct perioperative testing as claimed.

Second, Quane does not teach "genes" as the Examiner alleges in error. Quane teaches polymorphisms in one gene only (RYR1).

Third, the Quane reference relates to only one condition or phenotype, i.e. MH. Alone, or in combination with the Examiner's other references, Quane does not teach two or more nucleic acid genetic markers in two or more genes associated with two or more conditions to generate a genomic profile of use in selecting a perioperative course of action.



Claim 101 does not teach the single gene or the single condition of Quane. Because the single gene and the single condition taught by the Quane reference is not taught by Claim 101, Claim 101 must be entered into allowance.

### CONCLUSION

For the foregoing reasons, Applicant submits that the Examiner's rejection of Claims 74-105 is erroneous, and reversal of the rejection is respectfully requested. Should the Examiner believe that a telephone interview would aid in the prosecution of this application Applicant encourages the Examiner to call the undersigned collect at (608) 218-6900.

Dated: July 23, 2004



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